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The predictive value of the antioxidative function of HDL for cardiovascular disease and graft failure in renal transplant recipients



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ABSTRACT

Background: Protection of low-density lipoproteins (LDL) against oxidative modification is a key anti-atherosclerotic property of high-density lipoproteins (HDL). This study evaluated the predictive value of the HDL antioxidative function for cardiovascular mortality, all-cause mortality and chronic graft failure in renal transplant recipients (RTR).

Methods: The capacity of HDL to inhibit native LDL oxidation was determined in vitro in a prospective cohort of renal transplant recipients (RTR, n = 495, median follow-up 7.0 years).

Results: The HDL antioxidative functionality was significantly higher in patients experiencing graft failure ($57.4 \pm 9.7\%$) than in those without ($54.2 \pm 11.3\%$; $P = 0.039$), while there were no differences for cardiovascular and all-cause mortality. Specifically glomerular filtration rate ($P = 0.001$) and C-reactive protein levels ($P = 0.006$) associated independently with antioxidative functionality in multivariate linear regression analyses. Cox regression analysis demonstrated a significant relationship between antioxidative functionality of HDL and graft failure in age-adjusted analyses, but significance was lost following adjustment for baseline kidney function and inflammatory load. No significant association was found between HDL antioxidative functionality and cardiovascular and all-cause mortality.

Conclusion: This study demonstrates that the antioxidative function of HDL (i) does not predict cardiovascular or all-cause mortality in RTR, but (ii) conceivably contributes to the development of graft failure, however, not independent of baseline kidney function and inflammatory load.

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1. Introduction

High density lipoprotein particles possess a number of anti-atherosclerotic functionalities such as promoting cholesterol efflux from macrophage foam cells or protecting low density lipoproteins (LDL) against oxidative modification [1–3], a major initiating factor in the process of atherosclerotic lesion development [4]. Indeed, large epidemiological studies in the general population demonstrated that plasma levels of HDL cholesterol (HDL-C) can serve as a biomarker for the atheroprotective potential of HDL

[5,6]. However, recent genetic studies as well as pharmacological intervention trials indicated that HDL-C levels as such do not uniformly predict cardiovascular disease (CVD) risk [2]. The focus in the cardiovascular field is therefore currently shifting from HDL-C quantity determinations to efforts to measure the quality of HDL, i.e. the functional properties of these lipoproteins [1,2,7].

Renal transplant recipients (RTRs) have an increased risk of atherosclerosis formation, resulting in a 4–6 fold higher CVD risk [8]. In addition, transplant vasculopathy, an atherosclerotic process of the vasculature of the transplanted kidney is a major cause for chronic renal transplant dysfunction, leading to graft failure [9,10]. This is a highly relevant clinical issue, since 5 years after transplantation about 50% of the patients have developed transplant vasculopathy, a number even increasing to 90% after 10 years [9]. However, especially in this group of patients, classical risk factors including HDL-C concentrations do not fully explain the increase in atherosclerosis risk [9], making it likely that changes in functional

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properties of HDL critically contribute.

Therefore, the aim of this study was to evaluate the predictive value of a selected anti-atherosclerotic key function of HDL, namely its antioxidative potential, for the risk of future CVD mortality, all-cause mortality and graft failure in a well-characterized cohort of renal transplant recipients. Our data demonstrate that a contribution of the anti-oxidative function of HDL especially to the development of graft failure is conceivable, however, not independent of baseline kidney function and inflammatory load.

2. Materials and methods

For an extended description please see [online supplement](#).

2.1. Study design and study population

For this prospective study we used an established patient cohort of adult renal transplant recipients from the outpatient clinic of the UMCG who have visited the hospital between August 2001 and July 2003 [11,12]. The study was approved by the local Medical Ethics Committee (METc2001/039) and written informed consent was obtained from all participants. All patients had a functioning renal graft with no complications for at least 1 year to exclude early immune-mediated rejection as a potential confounding factor. Patients with other comorbidities such as endocrine abnormalities other than diabetes, congestive heart failure or malignant disease were excluded. All relevant patient characteristics were collected from the “Groningen Renal Transplant Database”, medical records and with help of a self-report questionnaire. Of the 847 eligible patients, 606 volunteered to participate and were included in the cohort. Plasma samples were available from 517 patients, of which 22 were excluded due to acute inflammation at the time of blood sampling as evidenced by high CRP levels (above 15 mg/l), leaving 495, in which the antioxidative functionality of HDL was determined. In an alternative set of analyses (please see [online supplement](#)) patients with CRP levels above 10 mg/l were excluded ($n = 65$), leaving $n = 454$ patients for analysis.

2.2. Isolation of HDL and measurement of antioxidative functionality

To determine HDL-mediated protection against LDL oxidation, a previously published method was used [13]. Briefly, HDL was isolated by precipitation of apoB-containing lipoproteins as described [13,14]. For the antioxidation assay 2% of individual HDL preparations were added to native, unoxidized LDL particles (100 mg/dl final protein concentration), after which oxidation was induced by 6.3 μ l of 2.5 mM AAPH (2,2'-azobis [2-amidinopropane] dihydrochloride) followed by incubation at 37 °C for 10 h. After that thiobarbituric acid reactive substances (TBARS) were determined as a measure for the degree of LDL oxidation as detailed previously [13]. The HDL antioxidative capacity was calculated as the percent reduction in TBARS formation obtained with an individual HDL sample relative to a reaction to which only LDL and AAPH but no HDL had been added [13]. Higher values thus indicate better protection against LDL oxidation. The antioxidation assay for all samples was carried out at the same time and with the same badges of reagents to limit potential variation due to different assay conditions. We also compared apoB-depleted plasma with (i) respective lipoprotein-free plasma preparations ([Supplemental figure I](#)) and (ii) HDL isolated by sequential density ultracentrifugation ([Supplemental figures II and III](#)). These combined data indicate that with the sample preparation method used in our study the antioxidative function is to a substantial part due to the presence of HDL. The storage time of the samples was not statistically

associated with the results of the antioxidative function assay indicating that different length of storage is not a confounding factor.

2.3. Primary end points

The main outcome measure of this study is the antioxidative functionality of HDL, the primary end points are cardiovascular mortality, all-cause mortality, and graft failure. Graft failure was defined as return to dialysis therapy or retransplantation. A surveillance system ensured information on patient status and cause of death between inclusion and up to the year 2009 [12].

2.4. Statistical analysis

All statistical analyses were conducted using SPSS 20. Normally distributed continuous variables are given as mean \pm standard deviation, continuous variables with a skewed distribution as median [25th–75th percentile] and categorical variables by absolute numbers (percentages). Overall trends between antioxidative functionality and the three primary endpoints were tested for significant differences using student's *t*-test. Renal transplant recipients were divided into tertiles according to the antioxidative functionality of HDL (low, medium, and high) and stratified for gender. Baseline characteristics of the patients were analyzed and tested for differences among these three groups. One-way analysis of variance followed by Bonferroni post hoc test was used for normally distributed variables and the Kruskal-Wallis test followed by Mann-Whitney *U* test for variables with a skewed distribution. The Chi-square test was used to compare categorical data. Multivariate linear regression analyses were performed with inclusion of parameters with a *P*-value ≤ 0.1 between the tertiles of HDL antioxidative capacity into the model and by eliminating by step-by-step backward regression ($P \leq 0.05$). Subsequently, multivariate Cox regression analysis models were created to estimate the hazard ratios (HRs) and 95% CIs for all-cause mortality, cardiovascular mortality and graft failure. HRs are reported per 1-SD increase with 95% confidence intervals (CIs). Power calculations indicated that the minimum detectable HR based on an assumption of 90% power and a two-sided alpha significance of 0.05 was 0.77 for CVD mortality, 0.83 for overall mortality, and 0.75 for graft failure. A two-sided *P*-value of ≤ 0.05 was considered statistically significant.

3. Results

In this study the predictive value of HDL antioxidative functionality on the survival of patients as well as their kidney grafts was analyzed in 495 renal transplant recipients (mean age 51.6 ± 12.0 ; 54% male). Patients had a median follow-up of 7.0 years [6.3–7.5 years]. Within this period, 102 (21%) patients died, which was attributable to CVD in 54 patients (11%). A total of 46 (9%) patients experienced renal graft failure.

First, the antioxidative functionality at baseline was compared between patients with or without subsequent cardiovascular death, all-cause mortality and graft failure during follow-up. At baseline, patients who died due to cardiovascular causes did not have a significantly different antioxidative function ($56.0 \pm 9.7\%$) compared to those not experiencing cardiovascular death ($54.3 \pm 11.4\%$; $P = 0.236$). Further, in patients who died due to any cause, antioxidative functionality was also not significantly different ($56.1 \pm 9.1\%$) compared to those who survived ($54.0 \pm 11.6\%$; $P = 0.095$). However, renal transplant recipients who did not experience graft failure had a significantly lower antioxidative HDL function ($54.2 \pm 11.3\%$), compared to those with subsequent graft failure ($57.4 \pm 9.7\%$; $P = 0.039$). When using a cut-

off value for CRP of 10 mg/l, these differences were no longer statistically significant (please see [online supplement](#) for details).

Next, baseline characteristics of the patients were analyzed. For this purpose patients were divided into tertiles, based on their HDL antioxidative functionality stratified for gender: low 44.0% [39.4–48.9], medium 55.7% [53.2–57.9] and high 64.4% [61.5–67.6]. [Table 1](#) shows the relevant baseline parameters, for the complete data set see online supplement ([Supplemental Table 1](#)). Age of the renal transplant recipients was not found to differ according to antioxidative functionality. Patients with higher antioxidative capacity had higher plasma levels of total cholesterol ($P = 0.035$) and triglycerides ($P = 0.006$). Apolipoprotein A-I, a major protein component of HDL, was inversely related to antioxidative function ($P = 0.044$). Higher levels of hsCRP, thus higher inflammatory load, were found to be associated with better antioxidative capacities of HDL ($P = 0.006$). Differences in insulin concentration and insulin resistance (HOMA-IR) among the different groups divided according to antioxidative functionality were also detected. In addition, better anti-oxidative function was associated with lower glomerular filtration rate (eGFR), thus decreased kidney function.

Then multivariate linear regression analyses were performed to assess which variables are independently associated with antioxidative functionality of HDL. All parameters found to show a difference of $P < 0.10$ between the tertiles of HDL antioxidative capacity, were included in the analysis ([Table 2](#)). Antioxidative functionality had an independent association with eGFR, gender, plasma hsCRP and insulin concentration, however, the R^2 of the final model was 0.07.

Further, multivariate Cox regression analysis was carried out to obtain proportional hazard ratios and evaluate the independent contribution of antioxidative functionality to the risk of mortality and graft failure ([Table 3](#)). Antioxidative function of HDL did not have a significant relationship with all-cause ($P = 0.108$) or specific cardiovascular mortality ($P = 0.276$), a finding remaining unchanged after correction for age, gender, eGFR and CRP. On the other hand, antioxidative capacity was found to be significantly associated with the risk of graft failure ($P = 0.038$). After adjustment for age, this association did not change appreciably ($P = 0.035$). After additional adjustment for gender, this association was still strong, but lost formal statistical significance ($P = 0.056$). Following further adjustment for eGFR, and CRP the association with graft failure is lost.

Taken together, these results indicate that the antioxidative

functionality of HDL might contribute to the development of graft failure in RTR, however, not independent of eGFR and CRP.

4. Discussion

The results of this prospective study suggest that, at least in RTR, the antioxidative functionality of HDL might not have the potential to serve as a clinically relevant predictive biomarker for cardiovascular disease, all-cause mortality or the development of chronic graft failure. RTR were chosen, since in this patient group the pathophysiological mechanisms of CVD but also of chronic atherosclerosis-mediated graft failure are not well defined, however, traditional risk factors and specifically HDL-C cannot fully explain the increased risk [9,15,16]. In our reasoning, these observations increased the probability for changes in HDL function to have an impact. The most interesting finding of our study is that baseline antioxidative functionality predicts graft failure in RTR, at least in crude and age-adjusted models. Unexpectedly though, a better antioxidative HDL function was associated with a higher risk of graft failure. A potential explanation could be derived from the observation that this correlation was lost once either an even stricter cut-off value for plasma CRP was used (10 mg/l instead of 15 mg/l, for data please see [online supplement](#)) or after correcting for potential confounders, most importantly eGFR and CRP. Both, a decline in kidney function and an increased inflammatory load are conditions of increased in vivo oxidative stress [17,18]. It is primarily counterintuitive that higher oxidative stress is associated with better anti-oxidative function of HDL. However, this association could be conceivably caused by a compensatory response namely an attempt to increase antioxidative defense mechanisms to meet the increased demand as e.g. has been shown in smokers [19]. That this attempt remains unsuccessful could be due to a decrease in other HDL functions in proinflammatory conditions, such as cholesterol efflux and reverse cholesterol transport [2,20]. The plausibility of these considerations is clinically supported by a study showing that high CRP levels offset the tight inverse correlation between HDL-C and risk of atherosclerotic cardiovascular disease; the authors also interpreted their findings as indicative of inflammation decreasing the atheroprotective functionality of HDL [21]. However, to formally prove this point further studies are required. Also, it should be noted that an absolute number of 46 patients with graft failure is relatively low for statistical analysis; therefore, although in itself robust, the results should be treated with caution.

Table 1

Most relevant characteristics of renal transplant recipients divided into tertiles based on HDL antioxidative functionality and stratified for gender.

Parameters	Tertiles according to antioxidative functionality			P Value
	Low	Medium	High	
HDL Antiox. Function (%)	44.0 [39.4–48.9]	55.7 [53.2–57.9] ^b	64.4 [61.5–67.6] ^{b,d}	<0.001
Age of patient, years	52.7 [43.8–60.2]	53.8 [42.3–61.1]	52.8 [44.1–59.9]	0.705
Male gender, n (%)	90 (54.5)	90 (54.2)	89 (54.3)	1.000
BMI, kg/m ²	25.7 ± 4.4	25.8 ± 4.0	26.3 ± 4.3	0.469
Total Cholesterol, mmol/L	5.5 ± 1.0	5.6 ± 0.9	5.8 ± 1.2	0.035
Apolipoprotein A-I, g/L	1.6 ± 0.3	1.6 ± 0.3	1.5 ± 0.3 ^c	0.044
LDL Cholesterol, mmol/L	3.4 ± 1.0	3.6 ± 0.9	3.7 ± 1.1	0.098
HDL Cholesterol, mmol/L	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.125
Triglycerides, mmol/L	1.8 [1.3–2.6]	1.8 [1.4–2.3]	2.1 [1.5–2.9] ^{a,d}	0.006
Insulin, mmol/L	12.1 [8.7–17.9]	10.1 [7.7–12.9] ^b	10.9 [7.7–14.8] ^a	0.003
HOMA-IR	2.4 [1.7–4.0]	2.0 [1.5–2.9] ^b	2.3 [1.5–3.2]	0.006
hsCRP, mg/L	1.5 [0.6–3.4]	2.0 [0.9–4.4] ^a	2.2 [1.1–5.3] ^b	0.006
eGFR, mL/min/1.73m ²	49.2 ± 16.6	48.9 ± 15.4	43.7 ± 14.9 ^{b,d}	0.002

^a Tertile significantly different from first (low) tertile, $P < 0.05$.

^b Tertile significantly different from first (low) tertile, $P < 0.01$.

^c Tertile significantly different from second (medium) tertile, $P < 0.05$.

^d Tertile significantly different from second (medium) tertile, $P < 0.01$. Data are given either as mean ± SD or median [25th–75th percentile].

Table 2

Variables independently associated with antioxidative functionality of HDL.

	Beta	95% CI	Standardized beta	P Value
eGFR, mL/min/1.73m ²	−0.103	[−0.164; −0.042]	−0.146	0.001
Male gender, n (%)	3.083	[1.150; 5.017]	0.137	0.002
hsCRP, mg/L	2.621	[0.739; 4.504]	0.121	0.006
Insulin, mmol/L	−5.655	[−9.838; −1.472]	−0.116	0.008

Variables are listed in decreasing order of strength of association according to the value of the standardized beta.

Table 3

Hazard ratios for graft failure, cardiovascular mortality and all-cause mortality by antioxidative functionality of HDL.

	Graft failure (46 events)		Cardiovascular mortality (54 events)		All-cause mortality (102 events)	
	HR [95%CI] per 1-SD increase	P value	HR [95%CI] per 1-SD increase	P value	HR [95%CI] per 1-SD increase	P value
Model 1 (crude)	1.03 [1.00–1.06]	0.038 ^a	1.01 [0.99–1.04]	0.276	1.02 [1.00–1.03]	0.108
Model 2 (model 1 + age)	1.03 [1.00–1.06]	0.035 ^a	1.01 [0.99–1.04]	0.300	1.02 [1.00–1.03]	0.123
Model 3 (model 2 + gender)	1.03 [1.00–1.96]	0.056	1.01 [0.99–1.04]	0.314	1.02 [1.00–1.03]	0.128
Model 4 (model 2 + eGFR)	1.01 [0.98–1.04]	0.571	1.01 [0.98–1.03]	0.660	1.01 [0.99–1.03]	0.392
Model 5 (model 3 + hsCRP)	1.01 [0.98–1.04]	0.535	1.00 [0.98–1.03]	0.832	1.01 [0.99–1.03]	0.514

^a Statistically significant, $P < 0.05$.

Another potential impacting factor could be LCAT. LCAT is an enzyme, which is associated with HDL and is involved in modulating LDL oxidation [13,22]. We concluded from a previous study that increased LCAT activity contributes to an impaired antioxidative functionality of HDL [13]. The activity of LCAT itself is reduced with impaired kidney function or inflammation, both present in RTR [23,24]. In this scenario a reduced LCAT activity might result in improved antioxidative functionality of the HDL particle. However, LCAT levels were not determined in the present study.

Furthermore, the anti-oxidative function of HDL could be influenced by the administered medication. In our study a better HDL function tended to be associated with the number of anti-hypertensives as well as the use of calcineurin inhibitors. Although in the present work for the anti-hypertensive medication this trend was not confirmed for individual classes of drugs, previous studies suggested that at least β -blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor 1 antagonists can reduce oxidative stress and lipid peroxidation [25,26]. Calcineurin inhibitors on the other hand are rather thought to induce oxidative stress [27–29]. Taken together, although the association did not reach the level of statistical significance, it can not be excluded at present that medication contributes to the observations made in our study and, in a broader perspective, to findings in cohorts of RTR in general.

Another finding of our study worthwhile to point out is the U-shaped relationship between the HDL anti-oxidative function and HOMA-IR. Since blood glucose values (Supplemental table 1) did not differ between the different tertiles of HDL anti-oxidative functionality, this relationship seems primarily due to differences in circulating insulin levels. HDL has been shown to impact both, insulin secretion by pancreatic β -cells [30] as well as glucose uptake in the periphery by skeletal muscle [31]. However, the current study was not designed to specifically investigate a relationship between HDL function and parameters of glucose metabolism; therefore, a potential causality of our observation as well as the delineation of impacting factors remain unresolved. Future studies with a specific focus on glucose metabolism parameters would be required to clarify these points.

In general, studies addressing the prospective value of HDL function measurements on clinically relevant outcomes are scarce. There are thus far only two reports evaluating a different

functionality of HDL, namely cholesterol efflux, in predicting future cardiovascular mortality in the general population. Interestingly, in one the authors found, also against expectations, that a high cholesterol efflux capacity was associated with an increased risk for CVD and death [32], while in the other better efflux at baseline predicted lower CVD risk during follow-up [33]. Clearly, more research is needed to understand the complex relationship between factors determining HDL quality independent of HDL-C levels and the clinical significance of HDL function in different relevant settings, including changes in response to therapeutic intervention. It needs to be taken into account for the interpretation of HDL function studies that no gold standards are available for respective assays and not even for methods to isolate HDL [2]. Therefore, interpretation of each individual study depends on the assay conditions applied, the respective experimental read-outs and the methodology to isolate HDL, which are complex particles differing in size and carrying a diverse lipid and protein cargo [2]. In the present study we decided to use plasma after precipitation of apoB-containing lipoproteins, similar to studies by other groups addressing HDL anti-oxidative properties [14]. This method is suitable for large numbers of clinical samples, however, also leaves other components of plasma. At present we can not, based on the design of our study, formally exclude that these might contribute to the associations found in our analyses.

In conclusion, our study shows that the antioxidative functionality of HDL might not be a clinically relevant parameter to predict future cardiovascular or all-cause mortality in RTR as well as chronic graft failure. Graft failure was predicted in these patients to a certain extent, however, not independent of baseline kidney function and inflammatory load, and in a fashion that might be opposite to expectations. More research, also including other biologically relevant functions of HDL will be required to delineate the prospective value of HDL function for CVD and graft failure in RTR.

Disclosure

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2016.04.008>.

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